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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCGAW, MICHAEL M	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,913	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *98-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is identified in the filing papers as a divisional and as a CIP of Application Number 09/930,915. Applicant should review the priority information. Claims 1-78, 79-97 and 110-115 have been cancelled by preliminary amendment. Claims 98-109 are currently under examination.

Priority

Applicant's attention is directed to pages 1 and 4 of the Application Data Sheet (ADS). The first page of the ADS indicates that the application is a divisional while the fourth page indicates that the application is a CIP. MPEP 601, Section I provides "[i]f there is a discrepancy between the information submitted in an application data sheet and the information submitted elsewhere in the application, the application data sheet will control except for the naming of the inventors and the citizenship of the inventors."

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a

parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director

may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 98-109 are rejected under 35 U.S.C. 112, second paragraph, as incomplete. "If the base claim has been canceled, a claim which is directly or indirectly dependent thereon should be rejected as incomplete." (See MPEP 608.01(n) V) Claims 98-108 either depend upon cancelled claims 1, 18 and 42, or they depend upon claims which are further dependent upon one of these three claims. In the interest of compact prosecution claims 98-108 are being interpreted as including the limitations of cancelled claims 1, 18 and 42. Such treatment does not relieve applicant of a response to this rejection. Appropriate correction is required.

Claims 98-109 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "variant, analog or complement" in claims 98-100 are relative terms which renders the claim indefinite. Claim 98 is directed to "[a] nucleic acid that encodes a recombinant HBc protein molecule according to [canceled] claim 1, or a ***variant, analog or complement thereof***." (emphasis added).

Claims 99 and 100 are identical to claim 98 except in that they refer to claims 18 and 42, respectively. Claims 101-109 depend upon claims 98-100. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 112, ¶1

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 98-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 98 is directed to "[a] nucleic acid that encodes a recombinant HBc protein molecule according to [canceled] claim 1, or a ***variant, analog or complement thereof***." (emphasis added). Claims 99 and 100 are identical to claim 98 except in that they refer to claims 18 and 42, respectively. Claims 101-109 depend upon claims 98-100.

Applicant does not define what it means to be a variant, analog or complement of a nucleic acid encoding an HBc protein within the context of a molecule such as that

according to claim one. At one end of the spectrum, one could imagine a variant a differing by only a single substitution. Towards the other end of the spectrum, one could envision a hepatitis B core molecule from a different virus, such as woodchuck hepatitis B virus with no N-terminal cysteine, with or without an antigenic epitope, and one would still have a variant of that in claim 1. Even the wt sequence would constitute a variant of claim one. If one takes a complement to be something that hybridizes to the nucleic acid encoding the molecule of claim 1 under conditions of moderate strigency, then that could be a vast number of nucleic acids, especially when one considers that claim one allows for 20% conservatively substituted amino acids. This could include, for instance, molecules not having an N-terminal cys residue. Simply put, applicant does not teach how to use all variants, complements or analogs of the nucleic acids encoding the molecules of claims 1, 18 or 42, especially given the possible breadth of such nucleic acids.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 98-109 are rejected under 35 U.S.C. 102(b) as being anticipated by Zlotnick, et al.

Claim 98 is directed to "[a] nucleic acid that encodes a recombinant HBc protein molecule according to [canceled] claim 1, or a variant, analog or complement thereof." Claims 99 and 100 are directed to nucleic acid molecules according to canceled claims 18 and 42, respectively. Claims 101 to 103 add limitations to claims 98 to 100, respectively, concerning the vector to which the nucleic acid segment is linked.

Zlotnick et al. (1997) (Cited on applicant's IDS as A29) teach a recombinant hepatitis B core (HBc) protein molecule. On page 9556-57 Zlotnick teaches capsid protein constructs such as Cp*149 and Cp*150 using the expression vector pET11a and bacterial strain BL21 (*E. coli*).

The Merriam-Webster Medical Dictionary defines variant as "[o]ne that exhibits variation from a type, norm or wild type" An analog is something "that is structurally similar to another but differs slightly in composition..." Thus, Zlotnick's HBc protein molecule was a variant and/or analog of the molecules described in claims 1, 18 and 42. The specification does not define what it means to be "a variant, analog or complement" in reference to a molecule such as that defined in claim 1. The specification, on page 55 provides the following:

> A nucleic acid sequence (DNA sequence or an RNA sequence) that (1) itself encodes, or its complement encodes, a chimer molecule whose HBc portion from residue position 1 through 136, when present, is that of SEQ ID NOs: 246, 247, 248, 249, 250 or 251 and (2) hybridizes with a DNA sequence of SEQ ID NOs: 274, 275, 276, 277, 278 or 279 at least at moderate stringency (discussed above); and (3) whose HBc sequence shares at least 80 percent, and more preferably at least 90 percent, and even more preferably at least 95 percent, and most preferably 100 percent identity with a DNA sequence of SEQ ID NOs: 274, 275, 276, 277, 278 and 279, is defined as a DNA variant sequence.
>
> An analog or analogous nucleic acid (DNA or RNA) sequence that encodes a contemplated chimer molecule is also contemplated as part of this invention. A chimer analog nucleic acid sequence or its complementary nucleic acid sequence encodes a HBc amino acid residue sequence that is at least 80 percent, and more preferably at least 90 percent, and most preferably is at least 95 percent identical to the HBc sequence portion from residue position 1 through residue position 136 shown in SEQ ID NOs: 246, 247, 248, 249, 250 and 251. This DNA or RNA

> is referred to herein as an " analog of" or "analogous to" a sequence of a nucleic acid of SEQ ID NOs: 274, 275, 276, 277, 278 and 279, and hybridizes with the nucleic acid sequence of SEQ ID NOs: 274, 275, 276, 277, 278 and 279 or their complements herein under moderate stringency hybridization conditions.

Even if such limitations from the specification were incorporated in to the claims, Zlotnick would still teach variants or analogs of the molecules of claims 1, 18 and 42.

Claims 98-109 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshikawa, A. et al. (1993).

Applicant claims "[a] nucleic acid that encodes a recombinant HBC protein molecule according to claim 1 [or 18 or 42], or a variant, analog or complement thereof."

Yoshikawa, A. et al. (1993) *Journal of Virology*, 67(10) p. 6064-6070 teach chimeric Hepatitis B core particles carrying antigenic epitopes of hepatitis C virus core protein. Figure 1 on page 6065 shows some of the chimeric proteins created.

pHBCx0, the first of the constructs from the top of Fig. 1, contained the n-terminal 149 amino acids of HBc fused to the residues found as coded in the multiple cloning site of the vector. That chimera had a cys residue within 4 residues of the N-terminal end. That sequence was expressed and used as a control to test the efficacy of the HBc-HCV fusions. (See for instance fig. 2) That HBc chimera was recognized by anti-HBc antibody but not by anti-HCV antibody. The details of the plasmid constructs are as described on page 6064 of Yoshikawa, A. et al. The recombinant plasmids were expressed in *E. coli* cells.

Also created was the construct pHBCx1. This construct had the HCV core polypeptide (amino acid residues 1-180) fused to residue 149 of the HBc core molecule.

Bukh, J. et al. (1994) Proc Natl Acad Sci U S A. 91(17):8239-43 is cited as evidence that the HCV core protein contains a conserved cys residue at position 172. (See pg. 8242, fig. 2) Thus, pHBCx1 had a cys residue within 8 amino acids of the C-terminus of the HBc-HCV chimer. Additionally, pHBC1-91 included residues 1-91 of HCV core peptide. It appears that residue 91 is generally a cys residue, though this residue is not conserved across all genotypes. PHBC1-91 and pHBCx1 may bind nucleic acids by virtue of residues in the HCV core protein.

Yoshikawa, A. et al. teach two or more HBc core particle chimeras with cys residues at or near the C-terminal and definitely within about 30 residues of the C-terminal. One of the these displayed HCV core protein epitopes at the C-terminal end.

Thus, Yoshikawa, A. et al. teach a recombinant hepatitis B core (HBc) protein molecule, pHBCx0, which is up to about 515 amino acid residues in length (actually for pHBCx0 ~173 aa's) that contains an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that includes either a peptide-bonded heterologous epitope and/or contains a sequence of 135 residues of the N-terminal 150 HBc amino acid residues, contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], contains a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus.

The chimeric polypeptides self-assembled into particles (see fig 4, g 6068) and meet the limitation as to the conserved amino acids. The pHBCx0 particles produced by

Yoshikawa, A. et al. would be substantially free of binding to nucleic acids on expression in a host cell since the region from 150-183 (the protamine domain known to bind nucleic acid) was deleted. Applicant indicates in Example 6 on page 125 that HBc core molecules of 149 residues in length have added stability when a –terminal cysteine is added. That added stability can also come as a result of the cys residue in a sequence added to the C-terminal end. Therefore, particles produced from pHBCx0 would be more stable than particles formed from an otherwise identical HBc chimer that lacks the C-terminal cys or in which the C-terminal cys residue present in the chimer is replaced by another residue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 98-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995) in view of Zlotnick et al (1997).

Applicant's claims are as outlined above.

Pumpens (cited by applicant as A16) teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules of a variety of lengths up to about 515 amino acid residues in length. These chimers contain an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule (See for

instance Fig. 1, pg. 64) that include a peptide-bonded heterologous epitope (Table 1, page 66) or a heterologous linker residue for a conjugated epitope present in the HBC immunodominant loop (see page 69, col. 1, last paragraph). Pumpens discloses that HBc chimeras with c-terminal truncations are capable of self-assembly and do not bind or 'pack' nucleic acid. (page 67, col. 1).

Pumpens makes two critical points on page 67. First, Pumpens reports that "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." Second, that "foreign insertions [at this site] are not only possible but also exert a stabilizing effect on chimeric HBCΔ derivatives..." Pumpens does not teach adding a c-terminal cysteine residue to achieve the stabilizing effect.

Zlotnick et al. (1997) teach adding a c-terminal cysteine residue to achieve a stabilizing effect.(See pgs. 9556 and 9558) Zlotnick's HBc chimera contained the HBc sequence from position 135-149 with a terminal cysteine at position 150, thus meeting the dual limitations of a chimer that contains (1) a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus and one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]. Zlotnick clearly demonstrates that the c-terminal particles are more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) (see page 9558, col. 1, first and second full paragraphs).

One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining this various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability.

One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

Claims 98-109 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of copending Application No. 10/732,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-69 are drawn to the same subject matter, e.g., recombinant chimer HBC protein molecules that have C-terminal cysteines, self-assemble into particles, and have improved particle stability, as are claims 1-46 of 10/732,862, differing only in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Zhou, S. et al. (1992) *Journal of Virology*, 66(9) p. 5393-5398 teach that the cys residues of hepatitis B virus capsid protein is not essential for the assembly of viral core particles but can influence the stability of the core particles.

Stahl et al. (1993) *Proc. Natl. Acad. Sci.*, 86 p. 6283-6287 teach chimeric Hepatitis B core particles carrying antigenic epitopes of heterologous hepatitis B virus peptides. Figure 1 on page 6284 shows some of the chimeric proteins created. Many of the chimeras had both C-terminal and N-terminal fusions. Constructs such as HBcS111-156 had a C-terminal cys residue within one residue of the termini. The lengths of the constructs with the C-terminal cys residues varied from roughly 191 residues to 218 residues. Antigenicity of the constructs was shown on pages 6284-6285.

The particles produced by Stahl et al. would be substantially free of binding to nucleic acids on expression in a host cell since the region from 145-183 (the protamine domain known to bind nucleic acid) was deleted. Applicant indicates in Example 6 on page 125 that HBc core molecules of 149 residues in length have added stability when a –terminal cysteine is added. That added stability can also come as a result of the cys residue in a sequence added to the C-terminal end. Therefore, particles produced from

the constructs such as HBcS111-156 would be more stable than particles formed from an otherwise identical HBc chimer that lacks the C-terminal cys or in which the C-terminal cys residue present in the chimer is replaced by another residue.

U.S. Patent No. 5,990,085 ('085 patent) to Ireland et al. (cited as A5 by applicant) teaches an inhibin-HBc fusion protein molecule of less than 515 amino acid residues in length that contains an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule. This protein molecule included a peptide-bonded heterologous epitope (ie. the inhibin insertion), contained one cysteine residue at position 107 of the HBc molecule [C-terminal cysteine residue(s)]. It contained a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus. One of Ireland's HBc chimeras utilized an internal insertion site at amino acid position 78 (see col.7, line 41). This chimera had a C-terminal truncation, ending at position 144 relative to the HBc sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. McKelvey

Wednesday, September 22, 2004

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600